REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 43, 46, 47, 51 and 54 to 58, the only claims pending and currently under examination in this application.

Amendments

The Applicants have amended Claim 43 to clarify that the host is known to suffer from epilepsy. The Applicants have amended Claim 58 to correct a typographical error. As the above amendments introduce no new matter to the application, their entry by the Examiner is respectfully requested.

Rejections

35 U.S.C. § 112, 1st ¶

The specification was objected to, and Claims 43, 46, 47, 51 and 54-58 were correspondingly rejected, under 35 U.S.C. § 112, 1st ¶. In making this rejection, the Examiner asserts that the specification is non-enabling for the full scope of agents as claimed in the present methods.

The claimed methods are directed to treating or preventing epilepsy by administering an effective amount of a serine protease inhibitor.

In support of these claims, the Applicants provide data showing the activity of AEBSF in rats in the "Kindling Assay." See Examples III and IV, pages 17 and 18, of the specification. The Kindling Assay is an art accepted model of Epilepsy. These results demonstrate that AEBSF is effective in treating/preventing epilepsy.

Furthermore, the specification teaches that AEBSF is representative of a broad class of agents that are collectively known as Serine Protease Inhibitors. See page 6, line 27 to page 7, line 4 of the specification.

Based on studies in which the activity of AEBSF and other serine protease inhibitors are evaluated, one of skill in the art knows that the activity of AEBSF in a given assay is strongly indicative of the activity of other serine protease inhibitors in the assay. See e.g.: (1) Rideout et al., " Inhibitors of trypsin-like serine proteases prevent DNA damage-induced neuronal death by acting upstream of the mitochondrial checkpoint and of p53 induction," Neuroscience. 2001;107(2):339-52, where AEBSF and TLCK were shown to have analogous activity in the reported assay; (2) Singh et al., " Serine protease inhibitor causes F-actin redistribution and inhibition of calcium-mediated secretion in pancreatic acini," Gastroenterology. 2001 Jun;120(7):1818-27, where AEBSF and N(alpha)-p-tosyl-L-phenylalanine chloromethyl ketone (TPCK) were shown to have analogous activity in the reported assay; (3) Bestilny & Riabowol, "A role for serine proteases in mediating phorbol ester-induced differentiation of HL-60 cells," Exp Cell Res. 2000 Apr 10;256(1):264-71, where AEBSF, TLCK and TPCK were shown to have analogous activity in the reported assay; and (4) Stefanis et al., " Inhibitors of trypsin-like serine proteases inhibit processing of the caspase Nedd-2 and protect PC12 cells and sympathetic neurons from death evoked by withdrawal of trophic support," J Neurochem. 1997 Oct;69(4):1425-37, where AEBSF and TLCK were shown to have analogous activity in the reported assay. As such, one of skill in the art would expect, with a reasonable expectation of success, serine protease inhibitors other than AEBSF to act as AEBSF in the Kindling assay.

Accordingly, the claimed methods are fully enabled by the specification. As such, the objection to the specification and corresponding rejection of Claims 43, 46, 47, 51 and 54-58 under 35 U.S.C. § 112, 1st ¶ may be withdrawn.

In addition, 51 and 54 and 57-58 have been rejected under 35 U.S.C. § 112, 1st ¶ for the asserted reason that the specification has not enabled claims directed to

preventing epilepsy in a host. However, as described above, the specification does provide data showing the results of AEBSF in the rat kindling assay, an art accepted model of epilepsy. Based on the results reported in the specification, and the knowledge of those of skill in the art that AEBSF is representative of how serine proteases act in general, the specification is fully enabling for methods of preventing epilepsy. Accordingly, this rejection may be withdrawn.

35 U.S.C. § 103

Claims 43, 46, 47, 51 and 54-58 were rejected under 35 U.S.C. § 103 as being unpatentable over Freidrich, Okajima, Veronesi and Pinsky, in view of Kazmirowski. In making this rejection, the Examiner continues to assert that the cited primary references teach the general approach of treating neurological conditions with protease inhibitors, and the supplemental Kazmirowski reference discloses the specific aminobenzenesulfonyl compounds employed in the experimental section. As such, the Examiner reasons that what the applicants have done is merely elucidate the mechanism of a method that has been inherently practiced in the prior art, and therefore have not made a patentable invention.

However, all of the pending claims are directed to the treatment/prevention of epilepsy.

It is respectfully submitted that, absent the data provided in the present application and working exemplification, one of skill in the art would not have found it obvious to employ serine protease inhibitors for the treatment of epilepsy because the cited prior art references provide no suggestion or guidance as to the effectiveness of serine protease inhibitors in the treatment of epilepsy.

The claimed invention is based on the observed results of the Kindling Assays reported in the experimental section of the present application. The Kindling Assay employed by the Applicants is well accepted by those of skill in the art as a model of

human conditions that result from undesirable synaptic responsiveness, e.g. epilepsy. As such, the Kindling Assay employed by the Applicants is an art accepted model of human epilepsy and related disease conditions associated with increased synaptic drive and/or responsiveness. In fact, the Kindling Assay is the major art accepted model of epilepsy, and any other type of assay is generally not accepted as indicative of what will, and will not be, effective in treating epilepsy and related disorders. See e.g., McNamara JO, Psychiatry Clin Neurosci. (1995) 49(3):S175-8; McNamara et al., CRC Crit Rev Clin Neurobiol. (1985) 1(4):341-91; and Sutula TP, Epilepsia. (1990) 31 Suppl 3:S45-54.

In the work performed by the Applicants, the Applicants showed that serine protease inhibitors were effective in treating symptoms brought about in the Kindling Assays. As such, only **after** the Applicants showed that serine protease inhibitors are effective in the Kindling Assay would one of skill in the art have a reasonable expectation of success that serine protease inhibitors would exhibit any activity, much less desirable therapeutic activity, in treating epilepsy.

Turning now to the cited references, Freidrich provides experimental evidence directed to the use of antithrombin compounds to promote neurite growth. Showing that an agent increases neurite growth teaches nothing about whether it is useful in the treatment of epilepsy. As such, one of skill in the art would have no idea based on Freidrich as to whether serine protease inhibitors would have any effect, much less a therapeutic effect, on epilepsy, as is now claimed. As pointed out above, one of skill in the art can not know whether a particular type of agent will have activity therapeutic activity with respect to epilepsy unless a representative of that particular type of agent is tested in a Kindling Assay.

Okajima describes the use of antithrombin III for prevention and treatment of "motor functional disturbance, tissue injury, spinal injury, and spinal ischemia." Since Okajima reports no Kindling Assay data and does not even mention epilepsy, Okajima also fails to provide any indication that serine protease inhibitors will have any activity,

much less a therapeutic activity, with respect to the treatment of epilepsy as now claimed.

Veronesi reports using PMSF to protect rats from neurological damage following exposure to Mipafox. As such, this report is based on preventing damage following exposure to a neurotoxin. Since Veronesi is concerned with preventing the effects of a neurotoxin, Veronesi says nothing about epilepsy. Since Veronesi reports no Kindling Assay data and does not even mention epilepsy, this reference also fails to provide any indication that serine protease inhibitors will have any activity, much less a therapeutic activity, with respect to the treatment of epilepsy as now claimed.

Pinsky reports the effect of peptidase inhibitors on rats undergoing narcotic withdrawal. Since Pinsky is concerned with the effects of narcotic withdrawal, Pinsky says nothing about epilepsy. While Pinsky calls the symptoms "eleptiform," this merely describes the seizures, not the condition being treated, which is narcotic withdrawal. Since Pinsky reports no Kindling Assay data, this reference also fails to provide any indication that serine protease inhibitors will have any activity, much less a therapeutic activity, with respect to the treatment of epilepsy as now claimed.

As such, the primary references, i.e., Freidrich, Okajima, Veronesi and Pinsky, all fail to provide any guidance as to the activity of serine protease inhibitors with respect to treatment of epilepsy.

As Kazmirowski has been cited solely for the teaching of a specific class of compounds as serine protease inhibitors, Kazmirowski fails to make up the fundamental deficiencies in the primary references.

Accordingly, the presently pending as amended above are not obvious over the combined teaching of Freidrich, Okajima, Veronesi and Pinsky, in view of Kazmirowski and are therefore patentable over the combined teaching of these references.

Atty Dkt. No.: THUR001
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Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number THUR001.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: November 9, 2004

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